Fully-automated MRI quantification of lateral-ventricle volume and volume-change in patients with Alzheimer's disease

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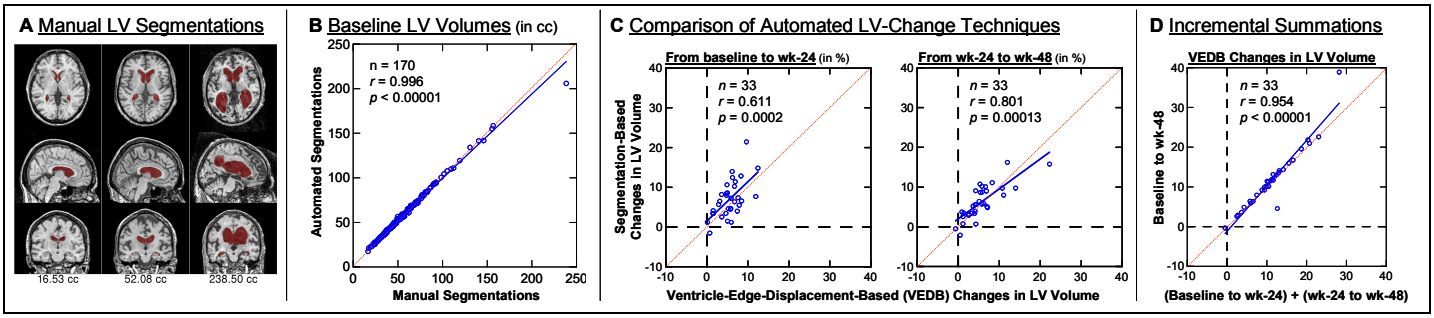
INTRODUCTION: Precise and accurate quantification of the volume, and the change in volume across time, of the lateral ventricles (**LV**) based on MRI data is an important goal in understanding the natural progression of neurodegenerative disorders such as Alzheimer's disease (**AD**) (*e.g.,* Nestor *et al.*, Brain. 2008;131:2443-54) and multiple sclerosis (**MS**) (*e.g.,* Dalton *et al.*, Neurology. 2006;66:693-8). Development of precise and accurate automated-segmentation techniques (*e.g.,* Schnack *et al.*, NeuroImage. 2001;14:95-104) is important in order to increase the efficiency, objectivity, and reliability of such quantifications of the LVs. In the present study, we addressed two issues related to such a goal. First, we examined the accuracy of a novel technique for the automated segmentation of the LVs in 270 patients with AD. Second, in a preliminary, representative subset of 33 of these patients, we assessed the concurrent validity, face validity, and precision of two novel techniques that we have developed for the automated quantification of longitudinal changes in the LV volumes of patients with AD.

METHODS: ***Subjects and Image Acquisition***: In the present study, we examined baseline MRI data from 270 elderly patients with mild to moderate AD acquired as part of an ongoing clinical trial. MRI data were acquired from 62 study sites using the following protocol: T1-weighted, RF-spoiled, gradient-recalled echo acquisition with TR = 22 ms, TE = 10 ms, flip angle = 30°, 250 mm field-of-view, 256 x 256 matrix and 110 sagittal partitions of 1.5 mm thickness. The resulting voxel size was 0.98 x 0.98 x 1.5 mm^3. Similarly-obtained wk-24 and wk-48 scans were also examined in the 33 patients included in the present assessment of our longitudinal metrics. ***Automated LV Segmentations***: As part of the clinical trial, the LVs in the patients' baseline scans were manually segmented on native-space data by expert readers at a central MRI reading center (NeuroRx Research, Montreal, Canada) according to well-specified criteria; examples of these can be seen in **Fig-A**. Data from these same scans were used to generate fully-automated LV segmentations using a novel technique, which takes about 15-20 minutes per scan and is based upon the combination of population-specific atlas warping (Grabner *et al.*, MICCAI, 2006;2:58) and label-fusion (Aljabar *et al.* NeuroImage. 2009;46:726-38) – the idea being that *(i)* the non-linear registration of a subject to the population-specific atlas should help to reduce the inter-subject anatomical variability, and *(ii)* the label-fusion technique should help to compensate for the residual variability and imperfectness of the registration technique. [As described elsewhere (Fonov *et al.*, submitted), the model used in this study was generated using data from a randomly-chosen "training" subset of 100 patients, tested in a different subset of 170 patients; as shown below, this produced highly accurate segmentations in those 170 test cases relative to their manual segmentations.] ***Longitudinal-Change Metrics***: Scans from the 33 patients included in the longitudinal analysis were quantified with regards to the changes in volume observed between wk-24 and baseline, wk-48 and wk-24, and wk-48 and baseline; this was done using two fully-automated techniques. In our *Segmentation-Based* (**SB**) technique, we calculated a simple %-change between the LV volumes generated by the aforementioned automatic-segmentation technique. Importantly, prior to this volume-change quantification, the automatically-generated LV volumes for each scan were normalized using the VSCALING factor obtained from a SIENAX analysis (Smith *et al.*, NeuroImage. 2002;17:479-89) of that same scan, which we previously showed to reduce the gradient-distortion effects associated with inconsistent Z-positioning of subjects across scans (Caramanos *et al.* NeuroImage. 2009; Epub ahead of print), which we have shown to be common in clinical trials and to affect the precision and accuracy of LV volume quantification (Caramanos *et al.*, Multiple Sclerosis. 2008;14(S1):S99). In our *Ventricle-Edge-Displacement-Based* (**VEDB**) technique, we used a more-sophisticated, fully-automated approach, which takes about 2 hours per comparison, to: *(i)* perform a non-brain-constrained, linear, symmetric registration between scans obtained at two timepoints; *(ii)* use a non-linear registration to create a subject-specific LV mask based on a LV mask generated at the 1st timepoint (in this case the manually-segmented baseline LV mask); *(iii)* calculate, with sub-voxel accuracy, the mean orthogonal motion between the two ventricular cerebrospinal-fluid and brain boundaries (which quantifies the change in LV volume); and *(iv)* express this change as a % of LV volume relative to the 1st timepoint – an approach based on that used by SIENA (Smith *et al.*, NeuroImage. 2002;17:479-89).

RESULTS: ***Accuracy of our Automated LV Segmentations***: As shown in **Fig-B**, a very strong linear relationship was found between the 170 testing-set LV volumes generated by the expert readers (*i.e.*, the manual segmentations that had not been used to train the model used by our automated segmentation technique) and by our automated segmentation technique ($r = 0.99$, $p < 0.00001$); furthermore, the masks generated by these segmentations were highly overlapping [Dice Kappa: mean (SD) range = 0.962 (0.015) 0.897 – 0.990] – supporting the accuracy of this automated approach. ***Concurrent and Face Validity of Our Longitudinal-Change Techniques***: As shown in **Fig-C**, there was a strong linear relationship between our two automated measures of longitudinal change in LV volume, both from baseline to wk-24 ($r = 0.61$, $p = 0.0002$) and from wk-24 to wk-48 ($r = 0.80$, $p < 0.00001$) – providing concurrent validity for these two different techniques. This was also true when looking at the change from baseline to wk-48 ($r = 0.61$, $p = 0.0002$). As expected given the nature of the patient population studied, significant increases in LV volume were found at all intervals for both techniques (series of *t*-tests of difference from 0, all with $p < 0.00001$); importantly, however, there was no significant interaction ($F_{1, 64} = 0.50$, $p = 0.482$) or main effect of Interval (*i.e.*, baseline-to-wk24 vs. wk24-to-wk48: $F_{1, 64} = 0.22$, $p = 0.640$) or Technique (*i.e.*, SB vs. VEDB: $F_{1, 64} = 1.57$, $p = 0.215$) on these increases – suggesting an equal degree of change across the two subsequent 24-wk intervals regardless of method used to quantify this change, and providing face validity and further concurrent validity for these two different techniques. ***Precision of Our VEDB Technique***: We used a three-time-point approach (Fox *et al*, J Mag Reson Imag. 1997;7:1069–75) to assess the precision of our VEDB technique via its incremental-change summation [*i.e.*, whether *(i)* the change from baseline to wk-48 was equal to *(ii)* the change from baseline to wk-24 added to the change from wk-24 to wk-48. Please note that this approach is not appropriate when combining cross-sectional measures, hence we did not apply this to the results of our SB technique]. As shown in **Fig-D**, our VEDB technique shows almost perfect incremental-change summation in almost all cases ($r = 0.95$, $p < 0.00001$) – suggesting a high level of precision for the estimates of LV-volume change generated by this technique.



DISCUSSION: In the present study, we have provided evidence for the accuracy of a novel, fully-automated, MRI-based technique for the segmentation of the lateral ventricles in patients with AD. Furthermore, we have provided preliminary evidence for the validity and precision of two novel, fully-automated, MRI-based techniques for the estimation of longitudinal change in the volume of the lateral ventricles in such patients.

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